THE TIME FOR NUPLAZID IS NOW

For your patients with PD psychosis

Indication

NUPLAZID is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Important Safety Information for NUPLAZID (pimavanserin)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.**

Please click Important Safety Information tab at top for additional safety information including **Boxed WARNING**.
Click tab at top for full Prescribing Information.

ONCE-DAILY
NUPLAZID®
(pimavanserin) 34mg capsules

PD PSYCHOSIS ADDS TO THE BURDEN OF CARING FOR A PATIENT WITH PD[1-3]

The hallucinations and delusions associated with PD psychosis can be serious and can progress[4]

The first sign was when Bob told Mary he saw their old dog, Toby, who had died 2 years before.

Actor portrayals

PD psychosis can impact both patients and their caregivers[2,3,5]

- Common delusions of jealousy and theft may cause patients to target their caregivers[6,7]
- Psychosis was the reason for 24% of hospital admissions for patients with PD[8]*
- Hallucinations (along with age, functional, and cognitive impairment) increased the risk of nursing home placement in patients with PD[9]

*In this retrospective review of patients with PD (N=143) over a 6-year period, symptoms of psychosis leading to hospitalization included frightening visual hallucinations (n=4), persecutory delusions with agitation and frightening hallucinations (n=18), and delirium (n=12). Motor complications were the reason for 37% of admissions.[8]

Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

Contraindication: NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported.

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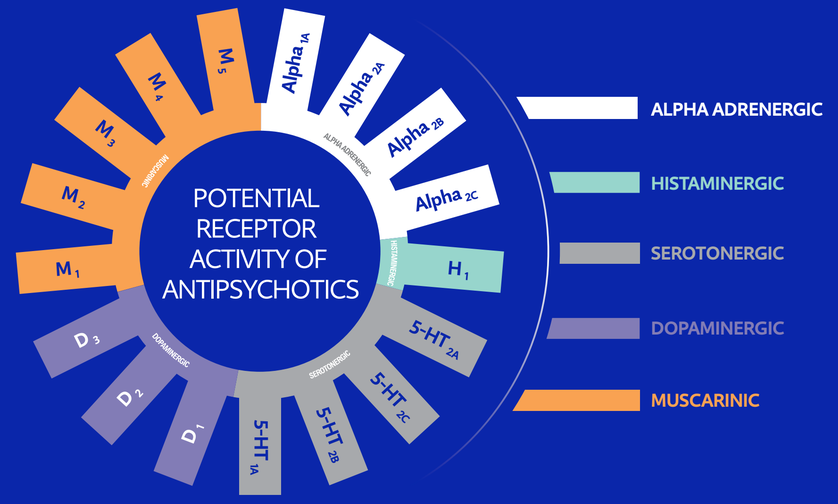
TREATMENT CONSIDERATIONS FOR PD PSYCHOSIS

Patients with PD psychosis are often treated with various antipsychotics, most of which are not FDA-approved for this use[10]

Antipsychotics may interact with various receptors[11]



The clinical relevance of potential receptor activity is unknown.

- Dopamine-receptor antagonism is associated with the potential to worsen PD motor symptoms[12]
- Serotonin plays a role in PD psychosis[13]

NUPLAZID is the only FDA-approved treatment indicated for delusions and hallucinations associated with PD psychosis[14,15]

Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

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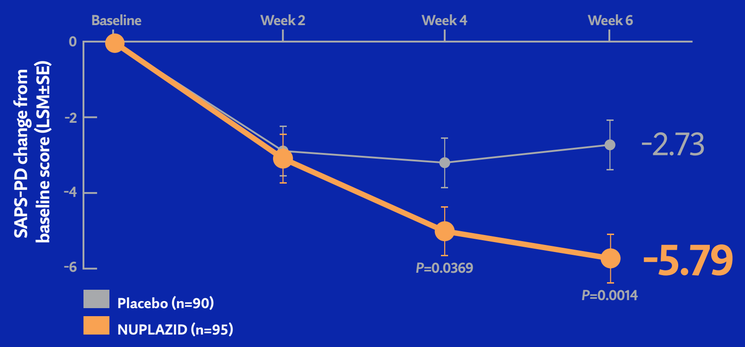
- NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.

ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

PROVIDES ROBUST EFFICACY

NUPLAZID significantly reduced the frequency and/or severity of delusions and hallucinations associated with PD psychosis at 6 weeks vs placebo (Primary Endpoint)[14]

NUPLAZID showed signs of improvement from baseline as early as 2 weeks, with significant reductions at Weeks 4 & 6[14,16]



SAPS-PD improvement from baseline

14% Placebo

vs

37% NUPLAZID

Results from a Phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel-group study of patients with PD psychosis (N=199). Primary endpoint was change from baseline in the 9-item SAPS-PD. Doses of PD medications taken prior to baseline were required to be stable 30 days prior to study start and throughout the study period. Mean baseline score was 15.9 for NUPLAZID and 14.7 for placebo.[14] The mean age of patients enrolled in the clinical study with NUPLAZID was 72 years. While the primary endpoint was designed to measure change from baseline to Week 6, a statistically significant difference between NUPLAZID and placebo was observed at Week 4 (*P*=0.0369) and again at Week 6 (*P*=0.0014).[16]

LSM=least squares mean; SAPS=Scale for Assessment of Positive Symptoms; SE=standard error.

NUPLAZID worked without impacting motor function or motoric activities of daily living vs placebo at Week 6[14,16]*

Mean change from baseline*: NUPLAZID -1.4 (n=92) vs placebo -1.7 (n=88).
(Placebo-subtracted difference [95% CI†] 0.3 [-2.1, 2.7].)

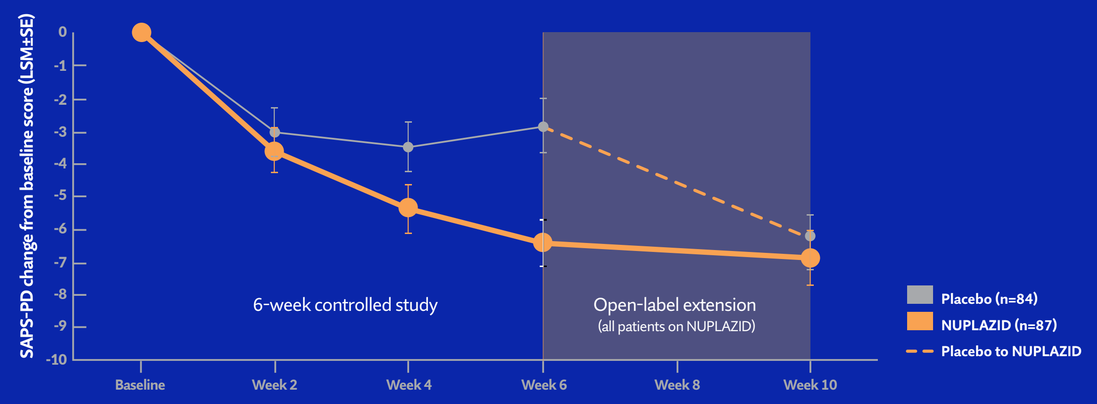
*Secondary endpoint as measured by Unified Parkinson's Disease Rating Scale Parts II and III.

†Noninferiority criteria required that the upper bound of the 95% CI not exceed 5.

SUSTAINED RESULTS OVER 10 WEEKS*

NUPLAZID efficacy results were sustained, with reductions in the frequency and/or severity of delusions and hallucinations continued from Week 6 through Week 10 in an open-label extension (OLE) of the study[17*†]

SAPS-PD change from core-baseline by visit[17]



*Of the 199 participants entering the Phase 3, 6-week, placebo-controlled study, 176 completed the 6-week study, and 171 entered the open-label extension (OLE) study. All patients received NUPLAZID 34 mg at Week 6 (baseline OLE) of the 10-week treatment period.[17]

Patients originally receiving placebo during the 6-week, double-blind phase saw a mean (SE) change from Week 6 to Week 10 of the treatment period in the SAPS-PD of -3.4 (0.7). For participants previously dosed with NUPLAZID 34 mg in the placebo-controlled study, the mean change from Week 6 to Week 10 of the treatment period for the SAPS-PD was -0.4 (0.8).[17,18]

†The 10-week treatment period includes 6 weeks of the placebo-controlled study plus the first 4 weeks of the OLE study. During the first 4 weeks of the OLE, patients and investigators remained blinded to the original treatment allocation from the placebo-controlled phase.[17]

Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

Adverse Reactions: The most common adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).

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Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

Drug Interactions:

- Coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole) increases NUPLAZID exposure. Reduce NUPLAZID dose to 10 mg taken orally as one tablet once daily.
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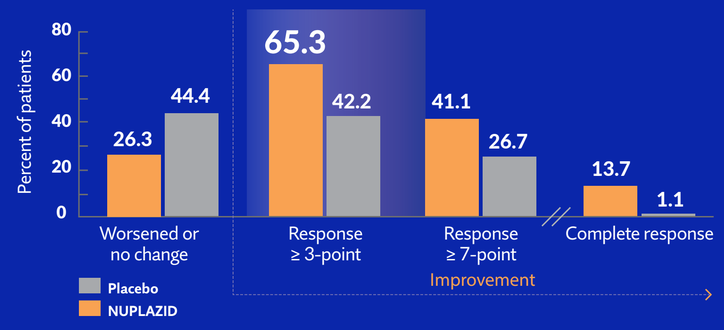
ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

REAL IMPROVEMENT FOR THE MAJORITY OF YOUR PD PSYCHOSIS PATIENTS

About 65% of NUPLAZID-treated patients experienced a clinically meaningful response vs 42% for placebo[14]*

Proportion of patients (responders) with SAPS-PD score improvement at end of Week 6 (N=185)[14]



~14% of NUPLAZID-treated patients experienced complete resolution of symptoms (SAPS-PD score reduced to 0 from baseline) vs 1% for placebo[14]

26% of NUPLAZID-treated patients experienced a worsening of, or no change in their SAPS-PD scores vs 44% for placebo[14]

Note: Complete response=SAPS-PD scores reduced to 0 from baseline value. Patients with missing values were counted as nonresponders.[14]

*Based on regression analysis, a clinically meaningful 1-unit change in the Clinical Global Impressions (CGI) scale was associated with a 2.33-point change in SAPS-PD.[7]

Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

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MEASURING THE EFFICACY OF NUPLAZID

SAPS-PD is a 9-item scale derived from SAPS that evaluates delusions and hallucinations in patients with PD psychosis[7]

TYPES OF DELUSIONS MEASURED[7]	TYPES OF HALLUCINATIONS MEASURED[7]
• Persecutory • Jealousy • Reference • Global rating of severity	• Auditory • Voices conversing • Somatic or tactile • Visual • Global rating of severity

Example SAPS Item: Global Hallucinations[19]

Scale	Severity	Patient response
0	None	
1	Questionable	
2	Mild	Hallucinations definitely present, but occur infrequently; at times the patient may question their existence
3	Moderate	Hallucinations are vivid and occur occasionally; they may bother the patient to some extent
4	Marked	Hallucinations are quite vivid, occur frequently, and pervade the patient's life
5	Severe	Hallucinations occur almost daily and are sometimes unusual or bizarre; they are very vivid and extremely troubling

Each item is scored on a scale of 0 (none) to 5 (severe), for a maximum score of 45.[14]

A 2.33-point change in the SAPS-PD is associated with clinically meaningful improvement—equivalent to a 1-point change in CGI-I[7]

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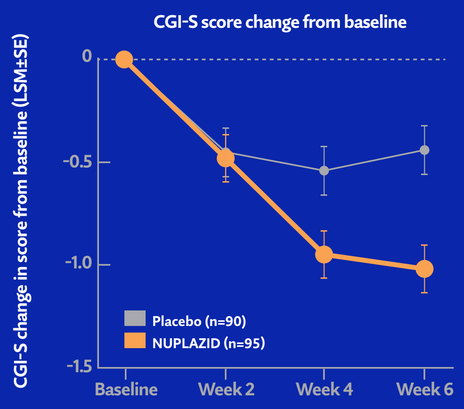
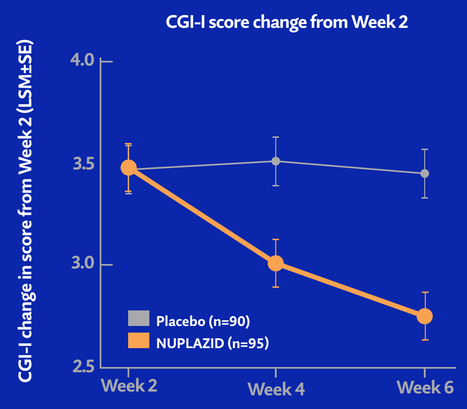
SUPPORTIVE EVIDENCE FOR NUPLAZID EFFICACY

Secondary Endpoints: NUPLAZID demonstrated greater improvement in Clinical Global Impressions (CGI) vs placebo[16*]

CGI-S (Severity) and CGI-I (Improvement) measured over 6 weeks[16]





- For the CGI-S, the mean change from baseline (SE) to Week 6 was -1.0 (0.1) for NUPLAZID vs -0.4 (0.1) for placebo.[†] A negative change in score indicates improvement[16]
- For CGI-I, the results at Week 6 were 2.8 (0.1) for NUPLAZID vs 3.5 (0.1) for placebo. A lower score indicates improvement[16]

A 1-point change in CGI is clinically meaningful.[7]

*Improvement was assessed by investigators who were blinded to SAPS-PD scores. SAPS-PD scores were strongly correlated with CGI scores: Spearman's rho CGI-S=0.5, CGI-I=0.6.[16]

†Change measured from mean baseline score of 4.3 for NUPLAZID and 4.3 for placebo.[16]

LSM=least squares mean; SE=standard error.

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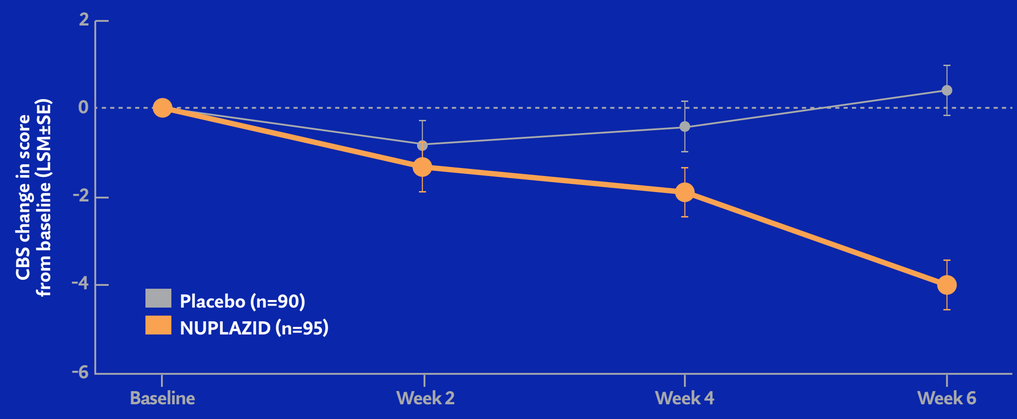
CAREGIVER BURDEN AND TREATMENT OF PD PSYCHOSIS

Exploratory Endpoint: At Week 6 caregivers of patients in the NUPLAZID group had a mean reduction in CBS score of -3.9 (1.0) compared with an increase of 0.4 (1.0) for caregivers of patients who received placebo[16*]

Zarit 22-item caregiver burden scale (CBS)[16†‡]



*Change measured from mean baseline score of 28.7 for NUPLAZID and 30.7 for placebo,[16] which is associated with a mild to moderate burden.[20]

†This exploratory analysis was not designed or powered sufficiently to draw treatment conclusions and is only informative. This could represent chance findings.

‡SAPS-PD scores were not correlated with change in Zarit caregiver burden score: Spearman's rho=0.3.[16]

Bob started accusing Mary of stealing his paints, or hiding them from him, which frightened her.

Actor portrayal

Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

Adverse Reactions: The most common adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).

DEMONSTRATED SAFETY IN PATIENTS WITH PD PSYCHOSIS

Adverse drug reactions experienced in the 6-week placebo-controlled clinical studies reported in ≥2% of patients and greater than placebo[14]

	NUPLAZID n=202	Placebo n=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	<1%
Psychiatric disorders		
Hallucination	5%	3%
Confusional state	6%	3%

In the 6-week placebo-controlled clinical studies:

- 8% (n=16) of patients treated with NUPLAZID discontinued due to adverse reactions vs 4% (n=10) with placebo[14]
  - The adverse reactions that occurred in more than one patient and with an incidence at least twice that of placebo were hallucination (2% NUPLAZID vs <1% placebo), urinary tract infection (1% NUPLAZID vs <1% placebo), and fatigue (1% NUPLAZID vs 0% placebo)
- Fewer cases of orthostatic hypotension were reported for NUPLAZID compared with placebo (1.0% NUPLAZID vs 5.2% placebo)[21]

No differences in safety were reported based on age, gender, or MMSE score (MMSE 21-24 vs ≥25)[14]

MMSE=Mini-Mental Status Examination.

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LONG-TERM SAFETY FINDINGS

Around 50% of patients continued on NUPLAZID for up to 1 year in an open-label extension (OLE) safety study[18]*

- 459 patients were enrolled in the OLE safety study
- The median duration of treatment was 454 days

No new or unexpected safety findings were observed in patients receiving NUPLAZID in an OLE study[18]

- The types of adverse events reported in an OLE study were comparable to the 6-week, placebo-controlled studies[18]
- Proportion of patients continuing NUPLAZID in the OLE study at[18]:
  - 1 month, 420 patients (92%); 3 months, 366 patients (80%); 6 months, 317 patients (69%); 1 year, 259 patients (56%); 2 years, 163 patients (36%); 3 years, 118 patients (26%); 4 years, 84 patients (18%)
- 19.2% of patients (n=88) discontinued study due to adverse events[18]

*The results of this OLE safety study should be interpreted with the following limitations: open-label design, lack of control arm, inability to assess patients long-term after discontinuation, and high discontinuation rate due to various reasons over >4 years of the study duration. This could represent chance findings.

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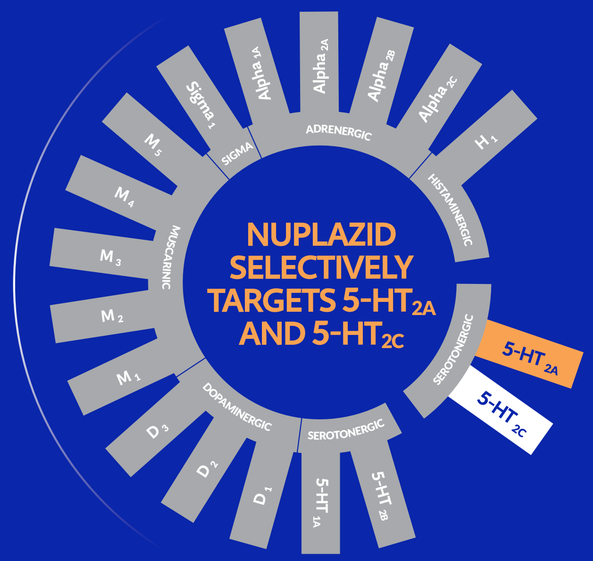
ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

THOUGHTFULLY DEVELOPED FOR YOUR RESIDENTS WITH PD PSYCHOSIS

In vitro, NUPLAZID is a serotonergic agent* with no appreciable affinity for dopaminergic, histaminergic, muscarinic, or adrenergic receptors.[14]



*The precise mechanism of action of NUPLAZID in the treatment of delusions and hallucinations associated with PD psychosis is unclear. However, the effect of NUPLAZID could be mediated through the combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors.[14]

Lower K_i numbers indicate a greater binding affinity and thus a smaller amount of the drug is needed to block activity.

NUPLAZID is recognized by the Movement Disorder Society as clinically useful for the treatment of psychosis in PD[22]

NUPLAZID is the first and only FDA-approved therapy for the treatment of delusions and hallucinations associated with PD psychosis.[14,15]

Mary told Bob's doctor about the delusions and hallucinations he was experiencing. That's when Bob was diagnosed with PD psychosis, and they learned about NUPLAZID.

Actor portrayals

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ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

CONVENIENT ONCE-DAILY DOSING

NUPLAZID 34 mg is[14]:

- **Taken orally**
- **No titration needed**
- **Taken with or without food**

1st

NUPLAZID is the first and only FDA-approved therapy proven to reduce delusions and hallucinations associated with PD psychosis[14,15]

DOSING AND ADMINISTRATION CONSIDERATIONS

(not actual size)

- Avoid the use of NUPLAZID in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval[14]*
- For patients taking strong CYP3A4 inhibitors, the recommended dose of NUPLAZID is 10 mg once daily[14]
- Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID[14]

NUPLAZID does not require a dosage adjustment in elderly patients, patients with mild to severe renal impairment or end-stage renal disease (ESRD)†, or in patients with hepatic impairment.[14]

The steady-state plasma concentration of NUPLAZID was reached in ~12 days with continuous treatment, without titration[21]

- Half-life ($t_{1/2}$) is 57 hours[14]

*In clinical studies, NUPLAZID prolonged the QT interval (mean increase ~5-8 ms).[14]

†Increased exposure (C_{max} and AUC) to NUPLAZID occurred in patients with severe renal impairment (CrCl <30 mL/min, Cockcroft-Gault) in a renal impairment study, NUPLAZID should be used with caution in patients with severe renal impairment and ESRD.[14]

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ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

NUPLAZID IS AFFORDABLE AND ACCESSIBLE

Comprehensive coverage and financial assistance make NUPLAZID affordable

100%
of Medicare Part D plans cover NUPLAZID[22]

85%
of Medicare Part D patients pay less than $10 for their NUPLAZID prescription*

$0
copay for commercially covered patients who qualify when enrolled in NUPLAZIDconnect™

NOTES

- For government-sponsored patients, NUPLAZIDconnect may be able to provide information regarding independent foundations and/or other resources that may help your patients
- If patients do not have insurance, or if their insurance does not cover NUPLAZID, they may be eligible to receive NUPLAZID for $0 through the NUPLAZIDconnect Patient Assistance Program†

Get your patients started on NUPLAZID right away with a free 14-day supply‡

*Around 15% of patients may pay more than $10 for their prescription. As reported by two representative specialty pharmacy organizations; Q1 2019 data.

†NUPLAZIDconnect patient eligibility and terms and conditions apply.

‡Appropriate patients must be enrolled in NUPLAZIDconnect to be eligible for the free 14-day supply of NUPLAZID. NUPLAZIDconnect patient eligibility and terms and conditions apply.

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PRESCRIBING NUPLAZID IS EASY

NUPLAZIDconnect makes it easy to start your patients on NUPLAZID

- **One simple step to start**
  - Complete a NUPLAZID treatment form
- **Or, prescribe directly to a NUPLAZID in-network specialty pharmacy and use CoverMyMeds®**
- **Our 5 participating in-network specialty pharmacies dispense and deliver NUPLAZID directly to your patients at a location of their choice**

NUPLAZIDconnect offers comprehensive patient support to provide them with a clear path forward, such as:

Navigating insurance and managing cost
- Offers a free 14-day supply of NUPLAZID‡
- Performs benefits verification
- Reviews coverage and financial support options, including referrals to independent foundations
- Provides a local NUPLAZIDconnect Access Manager who offers in-office education and resources to help facilitate access to the NUPLAZID you prescribed

Filling their prescription
- Works directly with specialty pharmacies to fill their prescription for NUPLAZID
- Clearly explains how NUPLAZID is filled and delivered to the patient

Educating your patient and their caregiver
- Answers NUPLAZID-related questions
- Helps to set expectations with your patient

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NUPLAZID connect™

ONCE-DAILY
NUPLAZID®
(pimavanserin) 34mg capsules

NUPLAZID INDICATION AND IMPORTANT SAFETY INFORMATION

Indication

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- **QT Interval Prolongation:** NUPLAZID prolongs the QT interval.
  - The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics or Class 3 antiarrhythmics, certain antipsychotic medications, and certain antibiotics.

Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

  - NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.
- **Adverse Reactions:** The most common adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).
- **Drug Interactions:**
  - Coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole) increases NUPLAZID exposure. Reduce NUPLAZID dose to 10 mg taken orally as one tablet once daily.
  - Coadministration with strong or moderate CYP3A4 inducers reduces NUPLAZID exposure. Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID.

Please click on the tab at top for full Prescribing Information, also available at NUPLAZIDhcp.com.

ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

THE TIME FOR NUPLAZID IS NOW

- **Proven to reduce the frequency and/or severity of delusions and hallucinations associated with PD psychosis[14]**
- **Demonstrated safety and tolerability profile for patients with PD psychosis[14]**
- **Recognized as clinically useful for the treatment of PD psychosis by the Movement Disorder Society[22]**

Mary and Bob are taking on his delusions and hallucinations due to PD psychosis together, with NUPLAZID. She says, "We spoke up, and it made all the difference."

Individual results may vary.

Actor portrayals

Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

QT Interval Prolongation: NUPLAZID prolongs the QT interval.

- The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics or Class 3 antiarrhythmics, certain antipsychotic medications, and certain antibiotics.
- NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.

Please click Important Safety Information tab at top for additional safety information including **Boxed WARNING.**
Click tab at top for full Prescribing Information.

ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

ACADIA® Pharmaceuticals

References: 1. Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Mental symptoms in Parkinson's disease are important contributors to caregiver distress. *Int J Geriatr Psychiatry*. 1999;14(10):866-874. **2.** Aarsland D, Bronnick K, Ehrt U, et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. *J Neurol Neurosurg Psychiatry*. 2007;78:36-42. **3.** Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al. Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. *Parkinsonism Relat Disord*. 2015;21(6):629-634. **4.** Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. The malignant course of "benign hallucinations" in Parkinson disease. *Arch Neurol*. 2006;63(5):713-716. **5.** Mack J, Rabins P, Anderson K, et al. Prevalence of psychotic symptoms in a community-based Parkinson disease sample. *Am J Geriatr Psychiatry*. 2012;20(2):123-132. **6.** Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord*. 2007;22(8):1061-1068. **7.** Voss T, Bahr D, Cummings J, Mills R, Ravina B, Williams H. Performance of a shortened Scale for Assessment of Positive Symptoms for Parkinson's disease psychosis. *Parkinsonism Relat Disord*. 2013;19(3):295-299. **8.** Klein C, Prokhorov T, Miniovitz A, Dobronevsky E, Rabey JM. Admission of Parkinsonian patients to a neurological ward in a community hospital. *J Neural Transm (Vienna)*. 2009;116(11):1509-1512. **9.** Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc*. 2000;48(8):938-942. **10.** Shim A, Frazer M, Skoog, B, Bancroft T, Cao F, Halpern R. Comparative adherence rates of antipsychotic therapies in patients with Parkinson's disease psychosis within the United States. Poster presented at: 5th World Parkinson Congress; June 4-17, 2019; Kyoto, Japan. Poster P20.08. **11.** Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*. 4th ed. New York, NY: Cambridge University Press; 2013. **12.** Goldman JG, Vaughan CL, Goetz CG. An update expert opinion on management and research strategies in Parkinson's disease psychosis *Expert Opin Pharmacother*. 2011;12(13):2009-2024. **13.** Ballanger B, Strafella AP, van Eimeren T, et al. Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol*. 2010;67(4):416-421. **14.** ACADIA Pharmaceuticals Inc. NUPLAZID® [package insert]. San Diego, CA; 2019. **15.** US Food and Drug Administration. FDA approves first drug to treat hallucinations and delusions associated with Parkinson's disease. www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-hallucinations-and-delusions-associated-parkinsons-disease. Updated March 1, 2019. Accessed January 14, 2020. **16.** Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*. 2014;383(9916):533-540. **17.** Isaacson SH, Coate B, Norton J, Abler V, Stankovic S. Improvement in SAPS-PD assessment over 10 weeks of pimavanserin treatment for Parkinson's disease psychosis. Poster presented at 3rd Pan American Parkinson's Disease and Movement Disorders Congress; February 15, 2020; Miami, Florida. **18.** Data on File (015), ACADIA Pharmaceuticals Inc. **19.** Andreasen NC. *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City, IA: University of Iowa; 1984. **20.** Zarit SH, Zarit JM. Instructions for the burden interview. University Park, PA: Pennsylvania State University; 1987. **21.** ACADIA Pharmaceuticals Inc. *NUPLAZID Advisory Committee Briefing Document*. San Diego, CA: Sponsor Background Information for a Meeting of the Psychopharmacologic Drugs Advisory Committee; March 29, 2016. www.fda.gov/media/96755/download. Accessed January 14, 2020. **22.** Seppi K, Chaudhuri KR, Coelho M, et al; on behalf of the Movement Disorder Society Evidence-Based Medicine Committee. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidenced-based medicine review. *Mov Disord*. 2019;34(2):180-198. **23.** Managed Markets Insight & Technology. Formulary Lookup website. www.formularylookup.com. Accessed January 14, 2020.

Pimavanserin is recognized as clinically useful for Parkinson's disease (PD) psychosis by the Movement Disorder Society (MDS)

MDS COMMISSIONED REVIEW

Update on Treatments for Nonmotor Symptoms of Parkinson's Disease—An Evidence-Based Medicine Review

Interventions to treat psychosis in PD†*				
DRUG	**EFFICACY**	**SAFETY†**	**PRACTICE IMPLICATIONS**	**FDA APPROVAL STATUS FOR PD PSYCHOSIS‡**
Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful	Not FDA approved
Olanzapine	Not efficacious	Unacceptable risk	Not useful	Not FDA approved
Quetiapine	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful‡	Not FDA approved
Pimavanserin	**Efficacious**	**Acceptable risk without specialized monitoring§**	**Clinically useful**	**FDA approved**

- This reflects the MDS commissioned review and is provided for educational purposes only. ACADIA does not recommend any drug for an indication not approved by the FDA
- Comparisons of efficacy or safety between or among drugs should not be drawn or inferred in the absence of head-to-head clinical data
- Please review full Prescribing Information for specific safety monitoring required for drugs listed above

RCTs=randomized controlled trials.

† The FDA mandates that antipsychotic drug manufacturers add black box warnings to labels and prescribing information because of the link found between antipsychotics and an increased mortality risk in elderly dementia patients. Moreover, antipsychotic medication may be associated with QT interval prolongation.

‡ Although there is insufficient evidence for quetiapine to be rated for the treatment of psychosis in PD, the practice implication is "possibly useful." There are no high-quality RCTs available for the treatment of quetiapine for psychosis in PD, and quetiapine was similarly efficacious to clozapine in the clozapine-controlled trials.

§ There is a lack of safety data regarding durability beyond 6 weeks. There were more serious adverse events in the pimavanserin arm (7.9%) when compared with the placebo arm (3.5%), but without a unifying pattern and as such, it is difficult to interpret these as drug related. Nevertheless, the FDA has very recently conducted an evaluation of available information about pimavanserin after the publication of reports of postmarketing adverse events. Based on the analysis of all available data, the FDA did not identify any new or unexpected safety findings with pimavanserin. After a thorough review, the FDA's conclusion remains unchanged that the drug's benefits outweigh its risks for patients with hallucinations and delusions of PD psychosis. Although the FDA did not identify any new or unexpected safety risks, there should be awareness of the possible adverse effects of pimavanserin including QT prolongation (especially with the concomitant use of other antipsychotic drugs or drugs that can cause QT prolongation) and a potential to cause a paradoxical worsening of symptoms.

*Used with permission of *Movement Disorders*, from Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Seppi, et al. *Mov Disord*. 34(2):2019; permission conveyed through Copyright Clearance Center, Inc.

Indication

NUPLAZID® (pimavanserin) is indicated for the treatment of delusions and hallucinations associated with Parkinson's disease psychosis.

Important Safety Information for NUPLAZID (pimavanserin)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.**

Please see additional Important Safety Information on the right.
Click tab at top for full Prescribing Information.

"Dose reductions of antiparkinsonian drugs to a level that will lead to a resolution of psychotic symptoms while maintaining sufficient symptomatic motor control is not always feasible and start of antipsychotic therapy becomes necessary."[1]

Important Safety Information for NUPLAZID (pimavanserin) (cont'd)

- **Contraindication:** NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported.
- **QT Interval Prolongation:** NUPLAZID prolongs the QT interval.
  - The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics or Class 3 antiarrhythmics, certain antipsychotic medications, and certain antibiotics.
  - NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.
- **Adverse Reactions:** The most common adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).
- **Drug Interactions:**
  - Coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole) increases NUPLAZID exposure. Reduce NUPLAZID dose to 10 mg taken orally as one tablet once daily.
  - Coadministration with strong or moderate CYP3A4 inducers reduces NUPLAZID exposure. Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID.

Please click on the tab at top for full Prescribing Information, also available at NUPLAZIDhcp.com.

References: 1. Seppi K, Chaudhuri KR, Coelho M, et al; on behalf of the Movement Disorders Society Evidence-Based Medicine Committee. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. *Mov Disord*. 2019;34(2):180-198. **2.** US Food and Drug Administration. FDA approves first drug to treat hallucinations and delusions associated with Parkinson's disease. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm498442.htm. Updated May 2, 2016. Accessed January 14, 2020.

ACADIA® Pharmaceuticals

MDS Review

ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

NUPLAZID® (pimavanserin) 34mg capsules

Treatment Form

NUPLAZID connect
Phone: 1-844-737-2223 • Fax: 1-844-737-2224
Long-term care phone: 1-877-889-0739
*Indicates required field.

See Indication and Important Safety Information including **Boxed WARNING** on the right.
Please complete and fax the Treatment Form to **1-844-737-2224** or email to **NUPLAZIDconnect@lashgroup.com**.
Please note that email communications sent to ACADIA or its third-party service providers may not be encrypted or secured, and safeguards established under the HIPAA Security Rule would not apply to these communications.

1 PATIENT INFORMATION/INSURANCE
Please fax copies of the front and back of drug insurance cards.

I have read and agree to HIPAA authorization on page 2 >> Patient signature Date

>> Signature of personal representative (if applicable) Date Description of authority

*Patient first name				Section required if patient has insurance	☐ Patient does not have insurance
*Patient last name				*Prescription drug plan	
*Address		*City		*Phone number	*ID number
*State	*ZIP code	*DOB (MM/DD/YYYY)	Gender	Plan number	Group number
*Patient phone number		*Preferred contact: ☐ Patient ☐ Caregiver		Cardholder name	
*Caregiver name				Relationship to cardholder	
*Patient email/Caregiver email				PCN / BIN Number	
*Caregiver phone number				Preferred language, if not English	

*Patient resides: ☐ At home ☐ Assisted Living ☐ Skilled Nursing Facility/Nursing Home

Preferred specialty pharmacy: ☐ Accredo ☐ Advanced Care Scripts ☐ AllianceRx Walgreens Prime ☐ CVS Specialty ☐ Humana ☐ Other_____

If "Assisted Living" or "Skilled Nursing Facility/Nursing Home" is selected, please complete the information below:

*Facility name		*Facility phone number	
Address	City	State	ZIP code
Facility contact name		Job title	
Pharmacy name		Pharmacy phone number	

2 PRESCRIBER INFORMATION

*Prescriber name	*Prescriber NPI number	State license number		
Practice/Facility name	*Address	*City	*State	*ZIP code
Primary contact name	*Phone number	*Fax		

Prescriber Authorization: I attest that I have obtained written permission that may be required under applicable federal and/or state law of my patient (or the patient's legal representative) for the release of my patient's Protected Health Information ("PHI") to ACADIA Pharmaceuticals, Inc. or its representatives or agents (collectively "ACADIA") as may be necessary for the patient's participation in a program designed to assist patients in determining their insurance coverage for NUPLAZID that I have elected to prescribe. I direct ACADIA to convey, on my behalf, the prescription and any prescription information delivered to ACADIA for NUPLAZID to the dispensing pharmacy chosen by or for the patient, to the patient's health insurance company, or to other third parties as may be necessary to assist this patient with filling his/her prescription for NUPLAZID, with securing any insurance coverage for NUPLAZID to which the patient is entitled, or other third parties to assist with patient assistance or reduced cost medication. I understand I am to comply with the state-specific prescription requirements such as e-prescribing, state-specific prescription form, fax language, etc. I agree that ACADIA may contact me for additional information relating to NUPLAZID, including but not limited to via email, fax and telephone. I authorize ACADIA to transmit the above prescription to the pharmacy.

>> Prescriber signature (No stamp allowed)_____ Date_____

3 DIAGNOSIS/PRESCRIPTION INFORMATION

*Please confirm diagnosis ☐ Hallucinations and delusions associated with Parkinson's disease (PD) psychosis (includes G20 Parkinson's disease) ☐ Other diagnosis_____
Coding must be to the highest level of specificity and all coding decisions are ultimately the responsibility of each prescribing health care professional.

*NUPLAZID® (pimavanserin) ONGOING PRESCRIPTION

NUPLAZID® (pimavanserin) ☐ Refills (# of refills):

☐ sig. Take 34 mg capsule orally, once daily ☐ Dispense: 30-day supply

☐ Other* # of days to be dispensed:

Substitution permitted >> Prescriber signature Date

Dispense as written >> Prescriber signature Date

*See Important Safety Information for dosing recommendations (including drug/drug interactions).

FREE 14-DAY SUPPLY OF NUPLAZID
Note: Limited to a 14-day supply per fill
(only for patients diagnosed with hallucinations and delusions associated with PD psychosis)

NUPLAZID® (pimavanserin) Refills (# of refills): 1

☐ sig. Take 34 mg capsule orally, once daily ☐ Dispense: 14-day supply

☐ Other # of days to be dispensed:

NUPLAZIDconnect™ may send a second Free 14-Day Supply if extra time is needed.

>> Prescriber signature Date

Note: Free 14-day Supply of NUPLAZID to be dispensed by TheraCom Pharmacy.
NUPLAZID will only be dispensed and delivered to facilities that accept free product.

HIPAA AUTHORIZATION 2

By signing this authorization, I authorize my health plans, physicians, long-term care and other health care providers, and pharmacies (collectively "Providers") to disclose my Protected Health Information ("PHI"), including, but not limited to, my name, address and phone number, information relating to my medical condition, treatment, care management, and health insurance, as well as information provided on this form and any prescription to ACADIA Pharmaceuticals Inc. and its representatives or agents (collectively "ACADIA"). I authorize and direct my Providers to make disclosures of PHI to ACADIA for the following purposes:

- Reimbursement support associated with the filling of my prescription for NUPLAZID, including the performance of an insurance verification and assisting in securing of any insurance coverage for NUPLAZID to which I am entitled
- Facilitating the provision of patient assistance, reduced cost medication and/or other NUPLAZID-related services offered by ACADIA
- Receiving marketing and promotional communications related to my disease condition, NUPLAZID, and other information from ACADIA. I hereby give consent to ACADIA, its affiliates and their agents and representatives, and my Providers to send communications and information to me via the contact information provided.

With respect to any disclosures by my pharmacies, I understand that my pharmacies will receive remuneration (payment) from ACADIA for making disclosures of PHI and/or support services to ACADIA; however, ACADIA agrees to protect my information and only use and disclose it for the purposes described above, or as I may further authorize in writing, or as required by law.

I understand that once my PHI is disclosed under this authorization, it is no longer protected by Federal privacy laws, including HIPAA, and may be further disclosed by ACADIA.

I understand that I may refuse to sign this authorization and that treatment, payment, or eligibility for benefits is not conditioned on my signing this authorization. I understand that I will be provided with a signed copy of this Authorization, by the Provider who collects it from me.

I understand that this authorization is valid for a period of 10 years or for a shorter period dictated by applicable state law.

I understand that I may cancel this authorization at any time by mailing a letter requesting such cancellation to NUPLAZIDconnect, PO Box 220305, Charlotte, NC 28222-0305, but that this cancellation will not apply to any information already used or disclosed through this authorization before notice of the cancellation is received by my Providers.

AUTHORIZATION TO DISCLOSE INFORMATION TO INDIVIDUALS INVOLVED IN MY CARE (optional)

I further authorize ACADIA Pharmaceuticals Inc., to discuss the coordination of my care with the following family member(s) and/or caregiver(s):

Authorized representative (1) Name (please print)_____ Relationship to patient_____

Authorized representative (2) Name (please print)_____ Relationship to patient_____

>> Patient signature/legal guardian signature_____ Date_____

Important Safety Information and Indication for NUPLAZID (pimavanserin)

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.**

- **Contraindication:** NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported.
- **QT Interval Prolongation:** NUPLAZID prolongs the QT interval.
  - The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics or Class 3 antiarrhythmics, certain antipsychotic medications, and certain antibiotics.
  - NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.
- **Adverse Reactions:** The most common adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).
- **Drug Interactions:**
  - Coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole) increases NUPLAZID exposure. Reduce NUPLAZID dose to 10 mg taken orally as one tablet once daily.
  - Coadministration with strong or moderate CYP3A4 inducers reduces NUPLAZID exposure. Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID.

Indication
NUPLAZID is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Dosage and Administration
Recommended dose: 34 mg capsule taken orally once daily, without titration.
NUPLAZID is available as 34 mg capsules and 10 mg tablets.

Please click on the tab at top for full Prescribing Information, also available at NUPLAZIDhcp.com.

ACADIA® Pharmaceuticals | NUPLAZID connect | ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

Treatment Form

ONCE-DAILY NUPLAZID® (pimavanserin) 34mg capsules

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUPLAZID safely and effectively. See full prescribing information for NUPLAZID.

NUPLAZID® (pimavanserin) capsules, for oral use
NUPLAZID® (pimavanserin) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. (5.1)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1)	06/2018
Dosage and Administration (2.2)	05/2019

----------INDICATIONS AND USAGE----------
NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose is 34 mg taken orally once daily, without titration. (2)
- Can be taken with or without food. (2)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 34 mg (3)
- Tablets: 10 mg (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to NUPLAZID or any of its components. (4)

----------WARNINGS AND PRECAUTIONS----------
- QT Interval Prolongation: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥5% and twice the rate of placebo): peripheral edema and confusional state. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ACADIA Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce NUPLAZID dose to 10 mg once daily. (2.2, 7.1)
- Strong or Moderate CYP3A4 Inducers: Avoid concomitant use of NUPLAZID. (2.2, 7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

NUPLAZID® is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

The recommended dose of NUPLAZID is 34 mg taken orally once daily, without titration.

NUPLAZID can be taken with or without food.

2.2 Dosage Modifications for Concomitant Use with CYP3A4 Inhibitors and Inducers

- Coadministration with Strong CYP3A4 Inhibitors
  The recommended dose of NUPLAZID when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) is 10 mg, taken orally as one tablet once daily *[see Drug Interactions (7.1)]*.
- Coadministration with Strong or Moderate CYP3A4 Inducers
  Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

NUPLAZID (pimavanserin) is available as:

- 34 mg strength capsules. The capsules are opaque white and light green with "PIMA" and "34" printed in black.
- 10 mg strength tablets. The orange, round, coated tablets are debossed on one side with a "P" and "10" on the reverse side.

4 CONTRAINDICATIONS

NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6- to 1.7-times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Boxed Warning]*.

5.2 QT Interval Prolongation

NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin) *[see Drug Interactions (7.1)]*. NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical trial database for NUPLAZID consists of over 1200 subjects and patients exposed to one or more doses of NUPLAZID. Of these, 616 were patients with hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In the placebo-controlled setting, the majority of experience in patients comes from studies evaluating once-daily NUPLAZID doses of 34 mg (N=202) compared to placebo (N=231) for up to 6 weeks. In the controlled trial setting, the study population was approximately 64% male and 91% Caucasian, and the mean age was about 71 years at study entry. Additional clinical trial experience in patients with hallucinations and delusions associated with PDP comes from two open-label, safety extension studies (total N=497). The majority of patients receiving long-term treatment received 34 mg once-daily (N=459). Over 300 patients have been treated for more than 6 months; over 270 have been treated for at least 12 months; and over 150 have been treated for at least 24 months.

The following adverse reactions are based on the 6-week, placebo-controlled studies in which NUPLAZID was administered once daily to patients with hallucinations and delusions associated with PDP.

Common Adverse Reactions (incidence ≥5% and at least twice the rate of placebo): peripheral edema (7% NUPLAZID 34 mg vs. 2% placebo) and confusional state (6% NUPLAZID 34 mg vs. 3% placebo).

Adverse Reactions Leading to Discontinuation of Treatment

A total of 8% (16/202) of NUPLAZID 34 mg-treated patients and 4% (10/231) of placebo-treated patients discontinued because of adverse reactions. The adverse reactions that occurred in more than one patient and with an incidence at least twice that of placebo were hallucination (2% NUPLAZID vs. <1% placebo), urinary tract infection (1% NUPLAZID vs. <1% placebo), and fatigue (1% NUPLAZID vs. 0% placebo).

Adverse reactions that occurred in 6-week, placebo-controlled studies and that were reported at an incidence of ≥2% and >placebo are presented in **Table 1**.

Table 1 Adverse Reactions in Placebo-Controlled Studies of 6-Week Treatment Duration and Reported in ≥2% and >Placebo

Percentage of Patients Reporting Adverse Reaction		
	NUPLAZID 34 mg	**Placebo**
	N=202	N=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	<1%
Psychiatric disorders		
Hallucination	5%	3%
Confusional state	6%	3%

Adverse Reactions in Demographic Subgroups

Examination of population subgroups in the 6-week, placebo-controlled studies did not reveal any differences in safety on the basis of age (≤75 vs. >75 years) or sex. Because the study population was predominantly Caucasian (91%; consistent with reported demographics for PD/PDP), racial or ethnic differences in the safety profile of NUPLAZID could not be assessed. In addition, in the 6-week, placebo-controlled studies, no clinically relevant differences in the incidence of adverse reactions were observed among those with a Mini-Mental State Examination (MMSE) score at entry of <25 versus those with scores ≥25.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of NUPLAZID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include rash, urticaria, reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea), somnolence, falls, agitation, and aggression.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with NUPLAZID

Table 2 Clinically Important Drug Interactions with NUPLAZID

QT Interval Prolongation	
Clinical Impact:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of NUPLAZID and increase the risk of cardiac arrhythmia.
Intervention:	Avoid the use of NUPLAZID in combination with other drugs known to prolong QT interval *[see Warnings and Precautions (5.2)]*.
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin, moxifloxacin
Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of NUPLAZID with a strong CYP3A4 inhibitor increases pimavanserin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	If NUPLAZID is used with a strong CYP3A4 inhibitor, reduce the dosage of NUPLAZID *[see Dosage and Administration (2.2)]*.
Examples:	itraconazole, ketoconazole, clarithromycin, indinavir
Strong or Moderate CYP3A4 Inducers	
Clinical Impact:	Concomitant use of NUPLAZID with strong or moderate CYP3A4 inducers reduces pimavanserin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID *[see Dosage and Administration (2.2)]*.
Examples:	Strong inducers: carbamazepine, St. John's wort, phenytoin, rifampin Moderate inducers: modafinil, thioridazine, efavirenz, nafcillin

7.2 Drugs Having No Clinically Important Interactions with NUPLAZID

Based on pharmacokinetic studies, no dosage adjustment of carbidopa/levodopa is required when administered concomitantly with NUPLAZID *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on NUPLAZID use in pregnant women that would allow assessment of the drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no adverse developmental effects were seen when pimavanserin was administered orally to rats or rabbits during the period of organogenesis at doses up to 10- or 12-times the maximum recommended human dose (MRHD) of 34 mg/day, respectively. Administration of pimavanserin to pregnant rats during pregnancy and lactation resulted in maternal toxicity and lower pup survival and body weight at doses which are 2-times the MRHD of 34 mg/day *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pimavanserin was not teratogenic in pregnant rats when administered during the period of organogenesis at oral doses of 0.9, 8.5, and 51 mg/kg/day, which are 0.2- and 10-times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC at mid and high doses, respectively. Maternal toxicity included reduction in body weight and food consumption at the highest dose.

Administration of pimavanserin to pregnant rats during pregnancy and lactation at oral doses of 8.5, 26, and 51 mg/kg/day, which are 0.14- to 14-times the MRHD of 34 mg/day based on AUC, caused maternal toxicity, including mortality, clinical signs including dehydration, hunched posture, and rales, and decreases in body weight, and/or food consumption at doses ≥26 mg/kg/day (2-times the MRHD based on AUC). At these maternally toxic doses there was a decrease in pup survival, reduced litter size, and reduced pup weights, and food consumption. Pimavanserin had no effect on sexual maturation, neurobehavioral function including

learning and memory, or reproductive function in the first generation pups up to 14-times the MRHD of 34 mg/day based on AUC.

Pimavanserin was not teratogenic in pregnant rabbits during the period of organogenesis at oral doses of 4.3, 43, and 85 mg/kg/day, which are 0.2- to 12-times the MRHD of 34 mg/day based on AUC. Maternal toxicity, including mortality, clinical signs of dyspnea and rales, decreases in body weight and/or food consumption, and abortions occurred at doses 12-times the MRHD of 34 mg/day based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pimavanserin in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUPLAZID and any potential adverse effects on the breastfed infant from NUPLAZID or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of NUPLAZID have not been established in pediatric patients.

8.5 Geriatric Use

No dose adjustment is required for elderly patients.

Parkinson's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the 6-week clinical studies with NUPLAZID *[see Adverse Reactions (6.1)]* was 71 years, with 49% 65-75 years old and 31% >75 years old. In the pooled population of patients enrolled in 6-week, placebo-controlled studies (N=614), 27% had MMSE scores from 21 to 24 compared to 73% with scores ≥25. No clinically meaningful differences in safety or effectiveness were noted between these two groups.

8.6 Patients with Renal Impairment

No dosage adjustment for NUPLAZID is needed in patients with mild to severe renal impairment or end stage renal disease (ESRD); however, increased exposure (C_{max} and AUC) to NUPLAZID occurred in patients with

severe renal impairment (CrCL <30 mL/min, Cockcroft-Gault) in a renal impairment study *[see Clinical Pharmacology (12.3)]*.

NUPLAZID should be used with caution in patients with severe renal impairment and end stage renal disease.

In a renal impairment study, dialysis did not appear to significantly affect the concentrations of NUPLAZID *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Hepatic Impairment

No dosage adjustment for NUPLAZID is recommended in patients with hepatic impairment based on the exposure differences observed in patients with and without hepatic impairment in a hepatic impairment study *[see Clinical Pharmacology (12.3)]*.

8.8 Other Specific Populations

No dosage adjustment is required based on patient's age, sex, ethnicity, or weight. These factors do not affect the pharmacokinetics of NUPLAZID *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

NUPLAZID is not a controlled substance.

9.2 Abuse

NUPLAZID has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence.

While short-term, placebo-controlled and long-term, open-label clinical trials did not reveal increases in drug-seeking behavior, the limited experience from the clinical trials do not predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

10 OVERDOSAGE

10.1 Human Experience

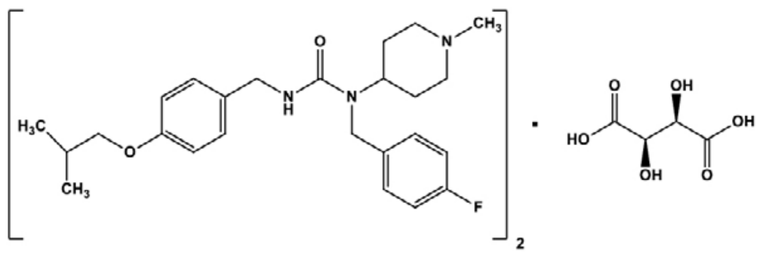
The pre-marketing clinical trials involving NUPLAZID in approximately 1200 subjects and patients do not provide information regarding symptoms with overdose. In healthy subject studies, dose-limiting nausea and vomiting were observed.

10.2 Management of Overdose

There are no known specific antidotes for NUPLAZID. In managing overdose, cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias *[see Warnings and Precautions (5.2)]*. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of NUPLAZID *[see Drug Interactions (7.1)]*. Consider the long plasma half-life of pimavanserin (about 57 hours) and the possibility of multiple drug involvement. Consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

11 DESCRIPTION

NUPLAZID contains pimavanserin, an atypical antipsychotic, which is present as pimavanserin tartrate salt with the chemical name, urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N*'-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1). Pimavanserin tartrate is freely soluble in water. Its molecular formula is $(C_{25}H_{34}FN_3O_2)_2 \cdot C_4H_6O_6$ and its molecular weight is 1005.20 (tartrate salt). The chemical structure is:



The molecular formula of pimavanserin free base is $C_{25}H_{34}FN_3O_2$ and its molecular weight is 427.55.

NUPLAZID capsules are intended for oral administration only. Each capsule contains 40 mg of pimavanserin tartrate, which is equivalent to 34 mg of pimavanserin free base. Inactive ingredients include magnesium stearate and microcrystalline cellulose. Additionally, the following inactive ingredients are present as components of the capsule shell: black iron oxide, FD&C blue #1, hypromellose, titanium dioxide, and yellow iron oxide.

NUPLAZID tablets are intended for oral administration only. Each round, orange, immediate-release, film coated tablet contains 11.8 mg of pimavanserin tartrate, which is equivalent to 10 mg pimavanserin free base. Inactive ingredients include magnesium stearate, pregelatinized starch, and silicified microcrystalline cellulose. Additionally, the following inactive ingredients are present as components of the film coat: polyethylene glycol, polyvinyl alcohol, red iron oxide, talc, titanium dioxide, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of pimavanserin in the treatment of hallucinations and delusions associated with Parkinson's disease psychosis is unclear. However, the effect of pimavanserin could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors.

12.2 Pharmacodynamics

In vitro, pimavanserin acts as an inverse agonist and antagonist at serotonin 5-HT_{2A} receptors with high binding affinity (K_i value 0.087 nM) and at serotonin 5-HT_{2C} receptors with lower binding affinity (K_i value 0.44 nM). Pimavanserin shows low binding to sigma 1 receptors (K_i value 120 nM) and has no appreciable affinity (K_i value >300 nM), to serotonin 5-HT_{2B}, dopaminergic (including D_2), muscarinic, histaminergic, or adrenergic receptors, or to calcium channels.

Cardiac Electrophysiology

The effect of NUPLAZID on the QTc interval was evaluated in a randomized placebo- and positive-controlled double-blind, multiple-dose parallel thorough QTc study in 252 healthy subjects. A central tendency analysis of the QTc data at steady-state demonstrated that the maximum mean change from baseline (upper bound of the two-sided 90% CI) was 13.5 (16.6) msec at a dose of twice the therapeutic dose. A pharmacokinetic/ pharmacodynamic analysis with NUPLAZID suggested a concentration-dependent QTc interval prolongation in the therapeutic range.

In the 6-week, placebo-controlled effectiveness studies, mean increases in QTc interval of ~5-8 msec were observed in patients receiving once-daily doses of NUPLAZID 34 mg. These data are consistent with the profile observed in a thorough QT study in healthy subjects. Sporadic QTcF values ≥500 msec and change from baseline values ≥60 msec were observed in subjects treated with NUPLAZID 34 mg; although the incidence was generally similar for NUPLAZID and placebo groups. There were no reports of torsade de pointes or any differences from placebo in the incidence of other adverse reactions associated with delayed

ventricular repolarization in studies of NUPLAZID, including those patients with hallucinations and delusions associated with PDP *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

Pimavanserin demonstrates dose-proportional pharmacokinetics after single oral doses from 17 to 255 mg (0.5- to 7.5-times the recommended dosage). The pharmacokinetics of pimavanserin are similar in both the study population and healthy subjects. The mean plasma half-lives for pimavanserin and the active metabolite (*N*-desmethylated metabolite) are approximately 57 hours and 200 hours, respectively.

Absorption

The median T_{max} of pimavanserin was 6 (range 4-24) hours and was generally unaffected by dose.
The bioavailability of pimavanserin oral tablet and pimavanserin solution was essentially identical.
The formation of the major circulating *N*-desmethylated metabolite AC-279 (active) from pimavanserin occurs with a median T_{max} of 6 hours.

Ingestion of a high-fat meal had no significant effect on rate (C_{max}) and extent (AUC) of pimavanserin exposure. C_{max} decreased by about 9% while AUC increased by about 8% with a high-fat meal.

Administration of one 34 mg capsule once daily results in plasma pimavanserin concentrations that are similar to exposure with two 17 mg tablets once daily.

Distribution

Pimavanserin is highly protein bound (~95%) in human plasma. Protein binding appeared to be dose-independent and did not change significantly over dosing time from Day 1 to Day 14. Following administration of a single dose of NUPLAZID (34 mg), the mean (SD) apparent volume of distribution was 2173 (307) L.

Elimination

Metabolism

Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and various other CYP and FMO enzymes. CYP3A4 is the major enzyme responsible for the

formation of its major active metabolite (AC-279). Pimavanserin does not cause clinically significant CYP inhibition or induction of CYP3A4. Based on *in vitro* data, pimavanserin is not an irreversible inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4).

Based on *in vitro* studies, transporters play no significant role in the disposition of pimavanserin.

AC-279 is neither a reversible or irreversible (metabolism-dependent) inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). AC-279 does not cause clinically significant CYP3A induction and is not predicted to cause induction of any other CYP enzymes involved in drug metabolism.

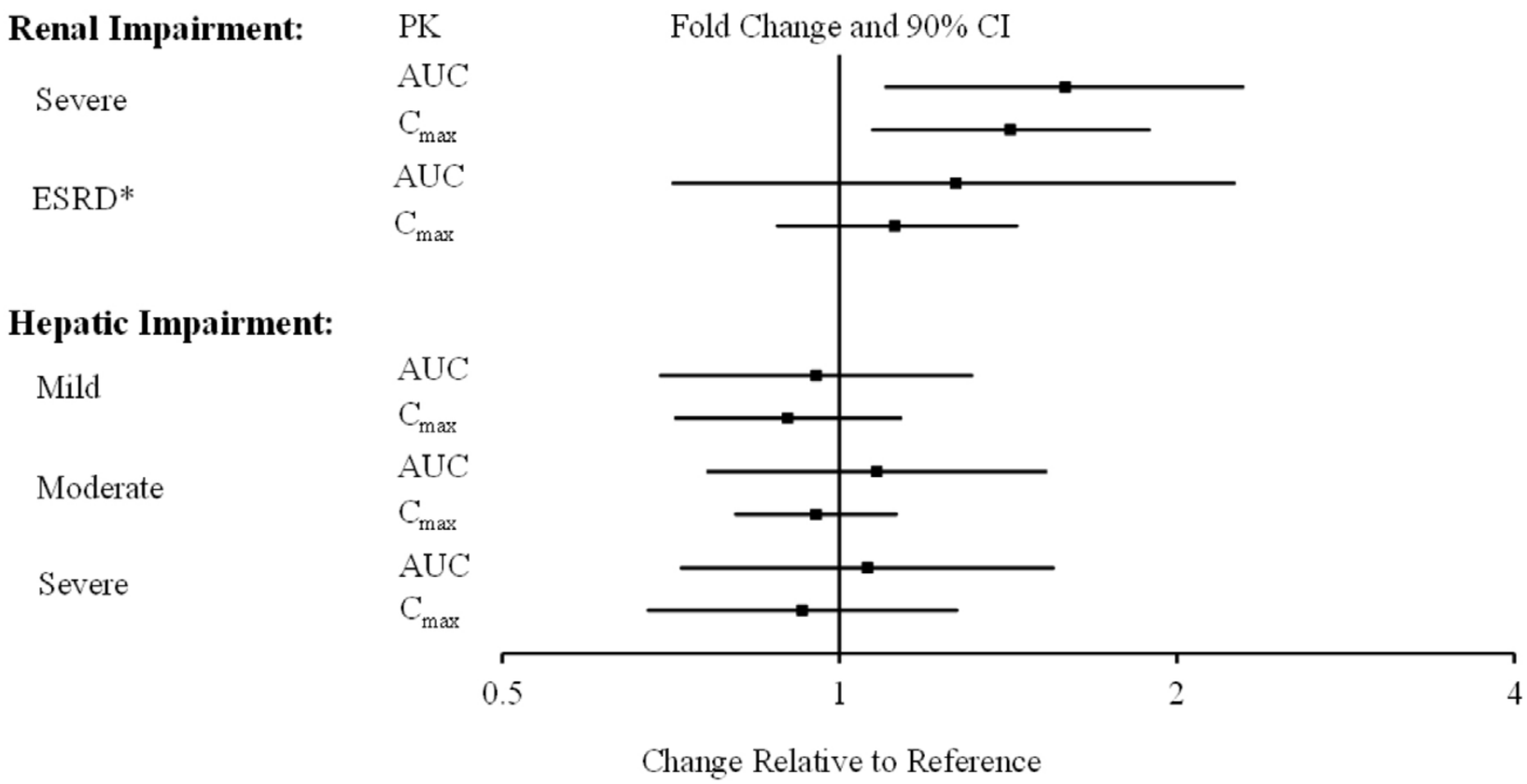
Excretion
Approximately 0.55% of the 34 mg oral dose of ^{14}C-pimavanserin was eliminated as unchanged drug in urine and 1.53% was eliminated in feces after 10 days.

Less than 1% of the administered dose of pimavanserin and its active metabolite AC-279 were recovered in urine.

Specific Populations
Population PK analysis indicated that age, sex, ethnicity, and weight do not have clinically relevant effect on the pharmacokinetics of pimavanserin. In addition, the analysis indicated that exposure of pimavanserin in patients with mild to moderate renal impairment was similar to exposure in patients with normal renal function.

The effects of other intrinsic factors on pimavanserin pharmacokinetics is shown in **Figure 1** *[see Use in Specific Populations (8.6 and 8.7)]*.

Figure 1 Effects of Intrinsic Factors on Pimavanserin Pharmacokinetics



*Less than 10% of the administered dose of NUPLAZID was recovered in the dialysate.

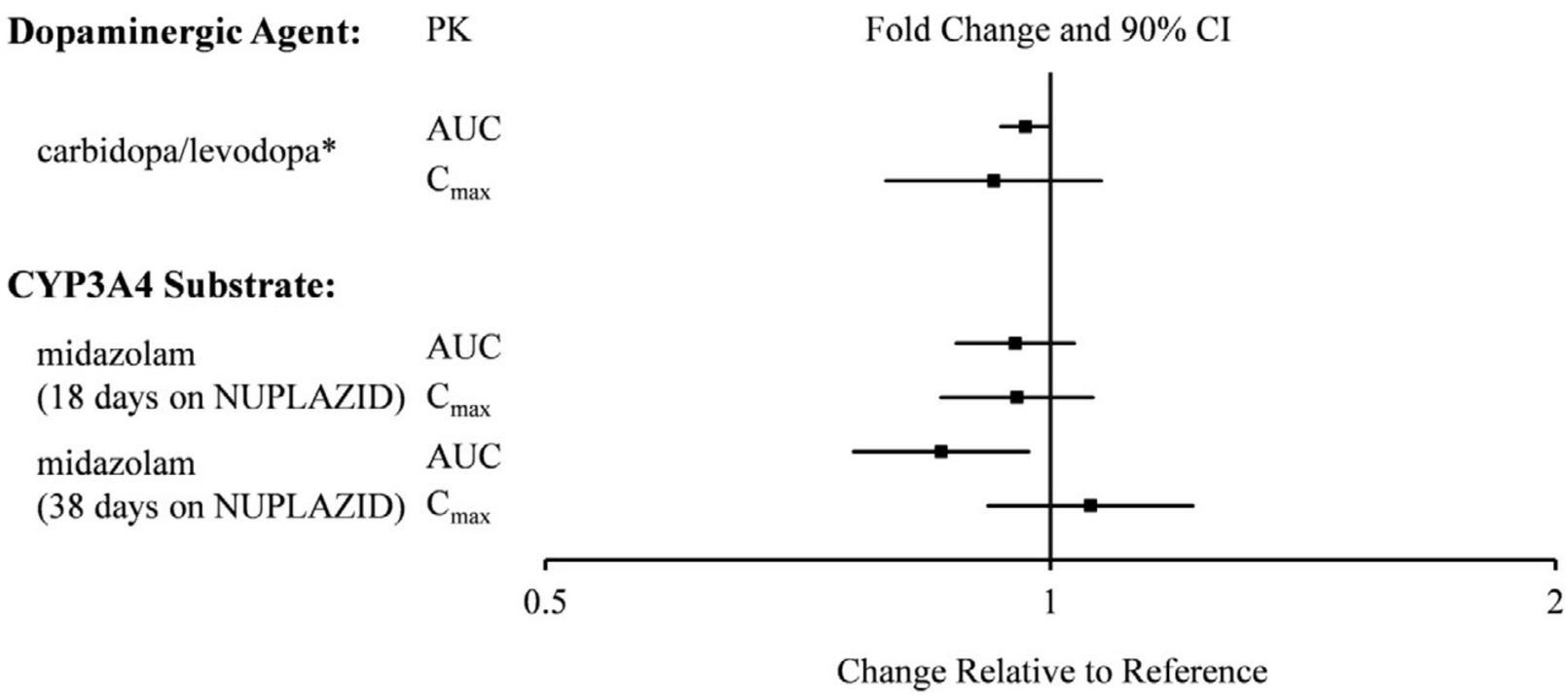
Drug Interaction Studies

CYP3A4 Inhibitor: ketoconazole, a strong inhibitor of CYP3A4, increased pimavanserin C_{max} by 1.5-fold and AUC by 3-fold. Population PK modeling and simulation show that steady-state exposure ($C_{max,ss}$ and AUC_{tau}) for 10 mg pimavanserin with ketoconazole is similar to exposure for 34 mg pimavanserin alone *[see Dosage and Administration (2.2) and Drug Interactions (7.1)]*.

CYP3A4 Inducer: In a clinical study where single doses of 34 mg pimavanserin were administered on Days 1 and 22, and 600 mg rifampin, a strong inducer of CYP3A4, was given daily on Days 15 through 21, pimavanserin C_{max} and AUC decreased by 71% and 91%, respectively, compared to pre-rifampin plasma concentrations. In a simulation with a moderate CYP3A4 inducer (efavirenz), physiologically based pharmacokinetic (PBPK) models predicted pimavanserin $C_{max,ss}$ and AUC_{tau} at steady state decreased by approximately 60% and 70%, respectively *[see Dosage and Administration (2.2) and Drug Interactions (7.1)]*.

There is no effect of pimavanserin on the pharmacokinetics of midazolam, a CYP3A4 substrate, or carbidopa/levodopa as shown in **Figure 2**.

Figure 2 Effects of Pimavanserin on the Pharmacokinetics of Other Drugs



*AUC and C_{max} depict levodopa levels.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of pimavanserin to mice or rats for 2 years. Mice were administered pimavanserin at oral doses of 2.6, 6, and 13 (males)/8.5, 21, and 43 mg/kg/day (females) which are 0.01- to 1- (males)/0.5- to 7- (females) times the MRHD of 34 mg/day based on AUC. Rats were administered pimavanserin at oral doses of 2.6, 8.5, and 26 (males)/4.3, 13, and 43 mg/kg/day (females) which are 0.01- to 4- (males)/0.04- to 16- (females) times the MRHD of 34 mg/day based on AUC.

Mutagenesis

Pimavanserin was not mutagenic in the *in vitro* Ames reverse mutation test, or in the *in vitro* mouse lymphoma assay, and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Pimavanserin was administered orally to male and female rats before mating, through mating, and up to Day 7 of gestation at doses of 8.5, 51, and 77 mg/kg/day, which are approximately 2-, 15-, and 22-times the maximum recommended human dose (MRHD) of 34 mg/day based on mg/m^2, respectively. Pimavanserin had no effect on fertility or reproductive performance in male and female rats at doses up to 22-times the MRHD of 34 mg based on mg/m^2. Changes in uterine parameters (decreases in the number of corpora lutea, number of implants, viable implants, and increases in pre-implantation loss, early resorptions and post-implantation loss) occurred at the highest dose which was also a maternally toxic dose. Changes in sperm parameters (decreased density and motility) and microscopic findings of cytoplasmic vacuolation in the epididymis occurred at doses approximately 15-times the MRHD of 34 mg/day based on mg/m^2.

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (foamy macrophages and/or cytoplasmic vacuolation) was observed in multiple tissues and organs of mice, rats, and monkeys following oral daily administration of pimavanserin. The occurrence of

phospholipidosis was both dose- and duration-dependent. The most severely affected organs were the lungs and kidneys. In rats, diffuse phospholipidosis was associated with increased lung and kidney weights, respiratory-related clinical signs including rales, labored breathing, and gasping, renal tubular degeneration, and, in some animals, focal/multifocal chronic inflammation in the lungs at exposures ≥10-times those at the maximum recommended human dose (MRHD) of 34 mg/day based on AUC. Phospholipidosis caused mortality in rats at exposures ≥16-times the MRHD of 34 mg/day based on AUC. The chronic inflammation in the rat lung was characterized by minimal to mild focal collagen positive fibroplasia as shown by specialized staining. Chronic inflammation of the lungs was not seen in monkeys treated for 12 months (exposures 9-times the MRHD). Based on the exposures at the estimated No Observed Effect Level (NOEL) for chronic lung inflammation in rats, there is a 5- to 9-times safety margin after 6-months of treatment and a 2- to 4-times safety margin after 24-months (lifetime) treatment compared to exposure at the MRHD. The relevance of these findings to human risk is not clear.

14 CLINICAL STUDIES

The efficacy of NUPLAZID 34 mg as a treatment of hallucinations and delusions associated with Parkinson's disease psychosis was demonstrated in a 6-week, randomized, placebo-controlled, parallel-group study. In this outpatient study, 199 patients were randomized in a 1:1 ratio to NUPLAZID 34 mg or placebo once daily. Study patients (male or female and aged 40 years or older) had a diagnosis of Parkinson's disease (PD) established at least 1 year prior to study entry and had psychotic symptoms (hallucinations and/or delusions) that started after the PD diagnosis and that were severe and frequent enough to warrant treatment with an antipsychotic. At entry, patients were required to have a Mini-Mental State Examination (MMSE) score ≥21 and to be able to self-report symptoms. The majority of patients were on PD medications at entry; these medications were required to be stable for at least 30 days prior to study start and throughout the study period.

The PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) was used to evaluate the efficacy of NUPLAZID 34 mg. SAPS-PD is a 9-item scale adapted for PD from the Hallucinations and Delusions domains of the SAPS. Each item is scored on a scale of 0-5, with 0 being none and 5 representing severe and frequent symptoms. Therefore, the SAPS-PD total score can range from 0 to 45 with higher scores reflecting greater severity of illness. A negative change in score indicates improvement. Primary efficacy was evaluated based on change from baseline to Week 6 in SAPS-PD total score.

As shown in **Table 3**, **Figure 3**, and **Figure 4**, NUPLAZID 34 mg (n=95) was statistically significantly superior to placebo (n=90) in decreasing the frequency and/or severity of hallucinations and delusions in patients with PDP as measured by central, independent, and blinded raters using the SAPS-PD scale. An effect was seen on both the hallucinations and delusions components of the SAPS-PD.

Table 3 Primary Efficacy Analysis Result Based on SAPS-PD (N=185)

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
SAPS-PD	NUPLAZID	15.9 (6.12)	-5.79 (0.66)	-3.06* (-4.91, -1.20)
	Placebo	14.7 (5.55)	-2.73 (0.67)	--
SAPS-PD Hallucinations[b]	NUPLAZID	11.1 (4.58)	-3.81 (0.46)	-2.01 (-3.29, -0.72)
	Placebo	10.0 (3.80)	-1.80 (0.46)	--
SAPS-PD Delusions[b]	NUPLAZID	4.8 (3.59)	-1.95 (0.32)	-0.94 (-1.83, -0.04)
	Placebo	4.8 (3.82)	-1.01 (0.32)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Supportive analysis.
* Statistically significantly superior to placebo.

The effect of NUPLAZID on SAPS-PD improved through the six-week trial period, as shown in **Figure 3**.

Figure 3 SAPS-PD Change from Baseline through 6 Weeks Total Study Treatment

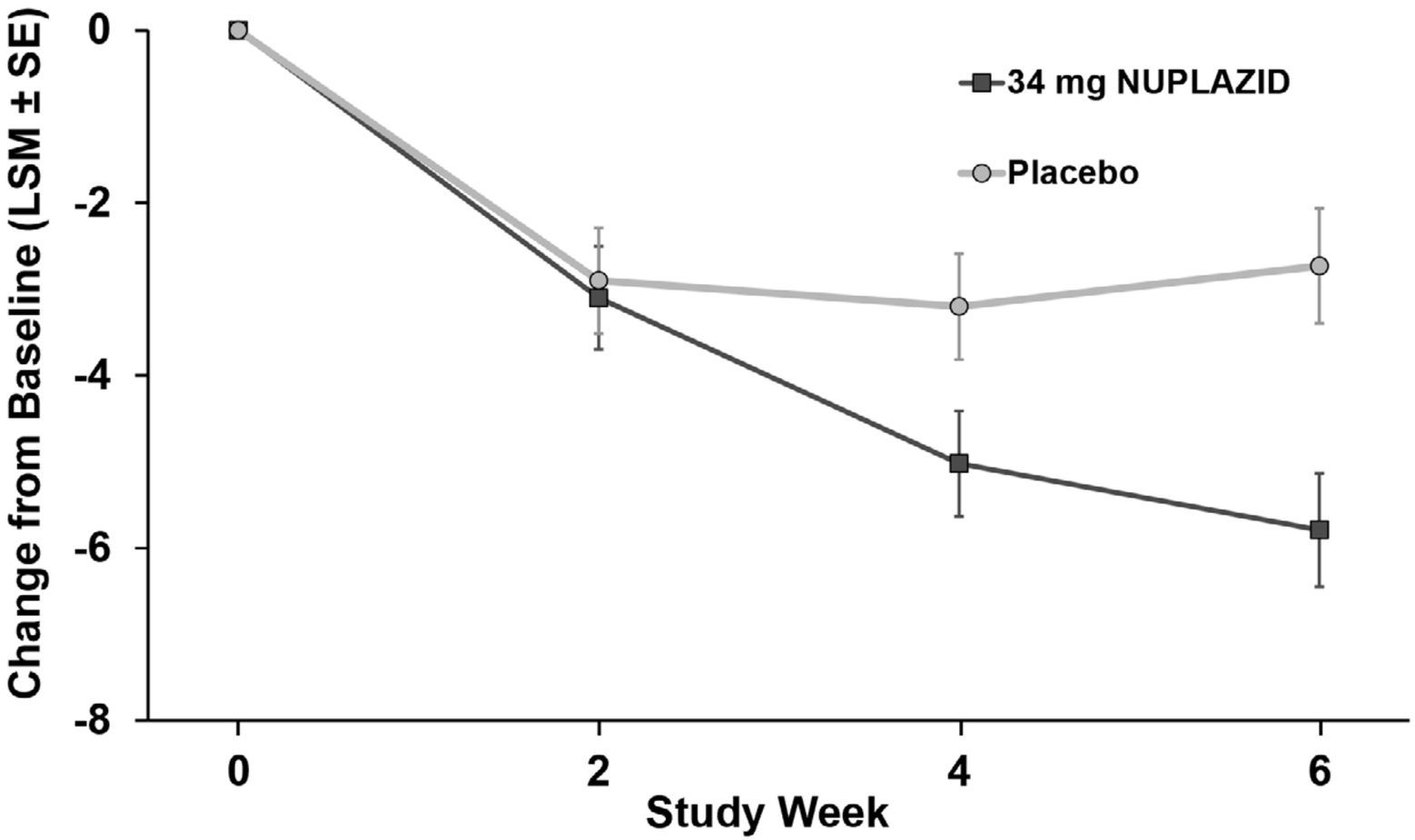
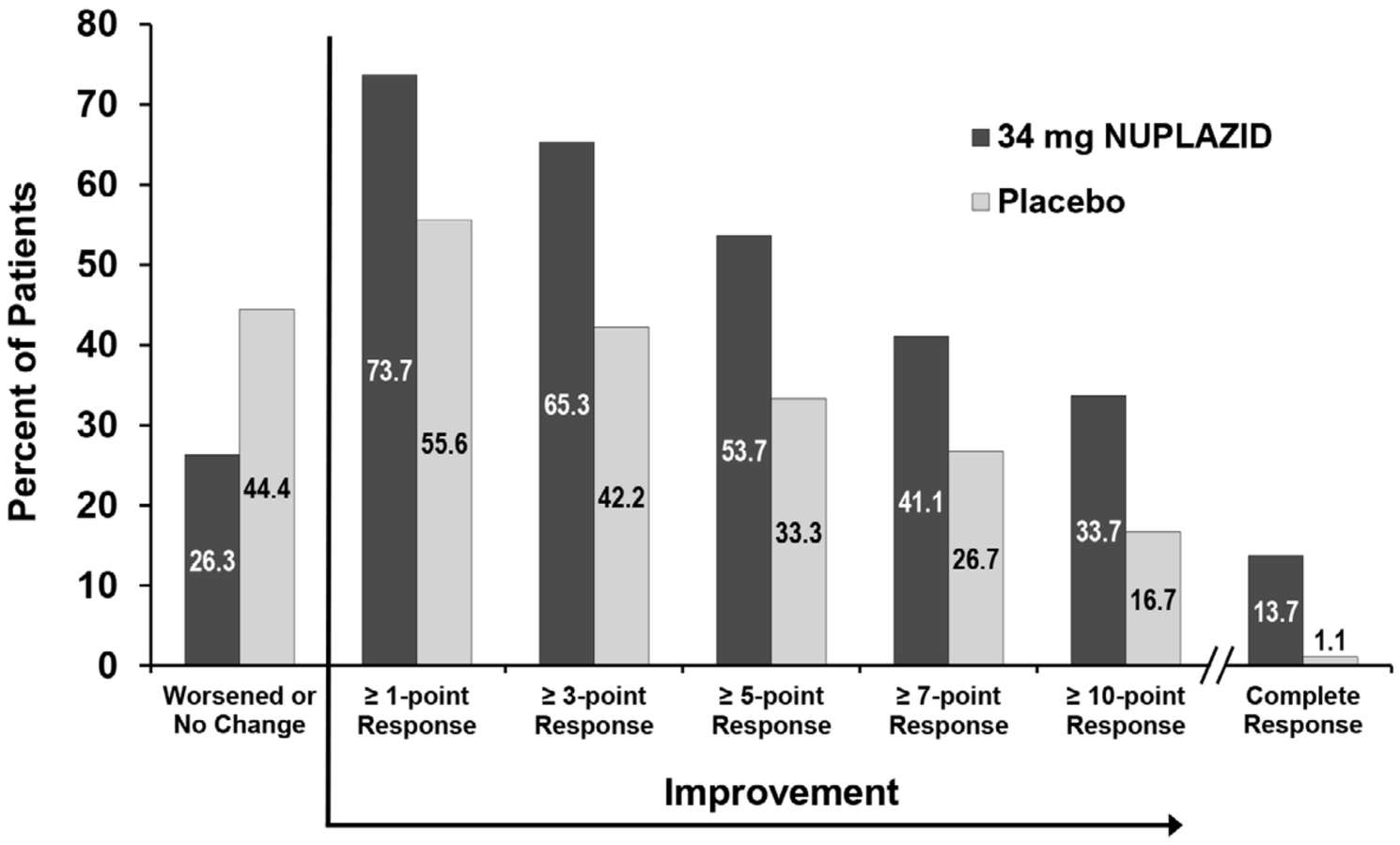


Figure 4 Proportion of Patients with SAPS-PD Score Improvement at the End of Week 6 (N=185)

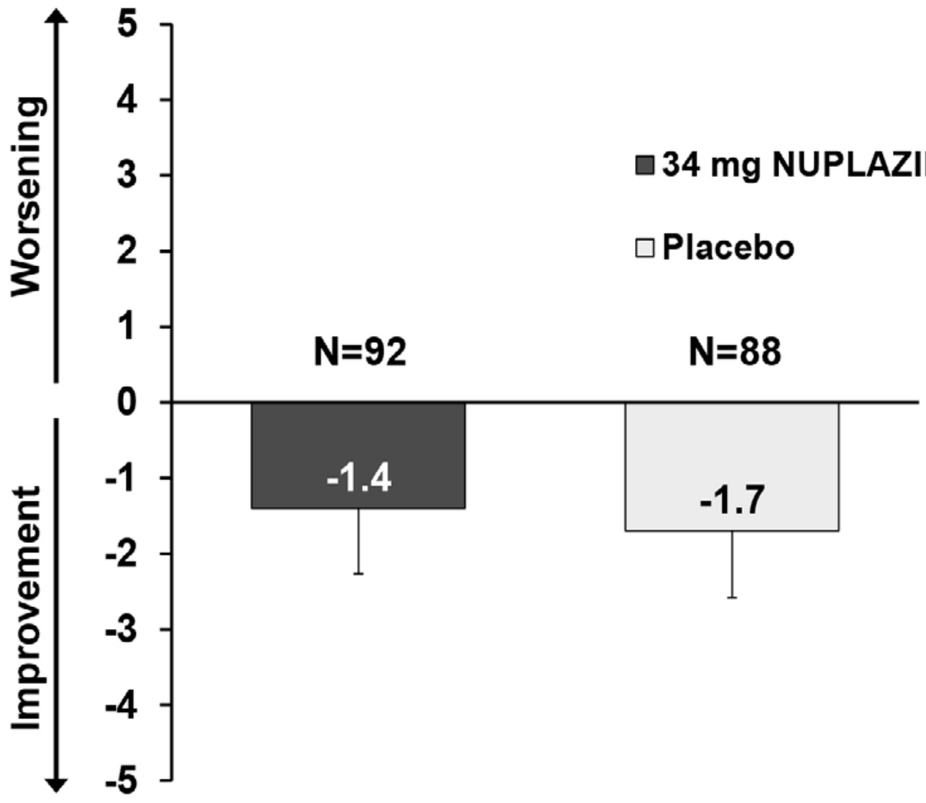


Complete response = SAPS-PD score reduced to zero from baseline value.
Patients with missing values were counted as non-responders.

Motor Function in Patients with Hallucinations and Delusions Associated with Parkinson's Disease Psychosis

NUPLAZID 34 mg did not show an effect compared to placebo on motor function, as measured using the Unified Parkinson's Disease Rating Scale Parts II and III (UPDRS Parts II+III) (**Figure 5**). A negative change in score indicates improvement. The UPDRS Parts II+III was used to assess the patient's Parkinson's disease state during the 6-week double-blind treatment period. The UPDRS score was calculated as the sum of the 40 items from activities of daily living and motor examination, with a range of 0 to 160.

Figure 5 Motor Function Change from Baseline to Week 6 in UPDRS Parts II+III (LSM - SE)



LSM: least-squares mean; SE: standard error. The error bars extend one SE below the LSM.

16 HOW SUPPLIED/STORAGE AND HANDLING

NUPLAZID (pimavanserin) is available as:

34 mg Capsule:
Opaque white and light green capsule with "PIMA" and "34" printed in black.
Bottle of 30: NDC 63090-340-30

10 mg Tablet:
Orange, round, coated tablet debossed with "P" on one side and "10" on the reverse.
Bottle of 30: NDC 63090-100-30

Storage
34 mg Capsule:
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. To prevent potential capsule color fading, protect from light.

10 mg Tablet:
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Concomitant Medication

Advise patients to inform their healthcare providers if there are any changes to their current prescription or over-the-counter medications, since there is a potential for drug interactions *[see Warnings and Precautions (5.2), Drug Interactions (7)]*.

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